RHÔNE-POULENC

Rhône-Poulenc Rorer

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March 19, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr.
Room 1-23
Rockville, MD 20852

Re: Docket No. 98D-0994
BACPAC I: Intermediates in Drug Substance Synthesis

Dear Sir:

Reference is made to the draft guidance for industry entitled "BACPAC I: Intermediates in Drug Substance Synthesis" which was published in the Federal Register: November 30, 1998 (Volume 63, Number 229), Docket No. 98D-0994. Rhône-Poulenc Rorer appreciates the opportunity to comment on this draft guidance.

Our comments are as follows:

General Comment

- For a site change, the guidance does not differentiate between testing and manufacturing site changes. Rhône-Poulenc Rorer recognizes that the subject of analytical testing laboratories is presented in the guidance document PAC-ATLS: Postapproval Changes - Analytical Testing Laboratory Sites. For purposes of clarity, Rhône-Poulenc Rorer suggests that the BACPAC I document cross-reference the PAC-ATLS document for direction on site changes for analytical testing laboratories.

- In cases where a mechanism for changing suppliers for starting materials is not defined in the NDA, no guidance was found in BACPAC I to indicate how such a change should be reported. Rhône-Poulenc Rorer requests FDA address this issue as part of the finalized guideline.

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98D-0994

Stability Testing for New Drug Applications

- **Lines 123 - 124** state that "The level of impurities should be established by comparing three postmodification batches to the range of historical data from ten premodification commercial batches."

  "Rhône-Poulenc Rorer suggests replacing this line with the following sentence: "*The level of impurities should be assessed by comparing three post-modification batches to historical data from a statistically significant number of consecutive pre-modification commercial batches or a combination of consecutive pre-modification batches that includes at least 3 consecutive commercial batches and 3 biobatchs, whichever is greater.*"

  Rhône-Poulenc Rorer makes this suggestion because for some processes of low dose commercially expensive material, the requirement for 10 premodification batches could represent several years of commercial production.

- **Lines 328 - 329** state that "Specification changes for the final intermediate are not included in this guidance." and **Lines 403 - 404** state that "Process changes that result in the formation of a different final intermediate are outside of the scope of this guidance."

  Rhône-Poulenc Rorer notes that this different treatment of the final intermediate appears inconsistent with the provision for other changes allowing a sponsor to demonstrate the equivalence on drug substance.

Rhône-Poulenc Rorer hopes that the comments provided will be helpful in finalizing this document. Should you have any questions regarding these comments please feel free to contact me at (610) 454-5498.

Sincerely,

Lelia A. Davenport
Senior Manager
Regulatory Affairs - CMC

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